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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/441,318	11/16/1999	PATRICIA L. CONKLIN	BTI-41	4166

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EXAMINER	
KUBELIK, ANNE R	

ART UNIT	PAPER NUMBER
1638	

DATE MAILED: 06/22/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/441,318	CONKLIN ET AL.	
	Examiner	Art Unit	
	Anne R. Kubelik	1638	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *22 April 2004*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-22 and 24-26* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-22 and 24-26* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *16 November 1999* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

1. Claims 1-22 and 24-26 are pending.

2. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

3. The provisional rejection of claims 1-22 and 24-26 under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-23 and 27 of copending Application No. 09/909,600 is withdrawn in light of the abandonment of that application.

Claim Objections

4. Claims 5-7, 12-14 and 20-21 are objected to under 37 CFR 1.75(c), as substantial duplicates of the parent claims 1, 9 and 16. See MPEP § 706.03(k). If transformation of a plant with a nucleic acid encoding phosphoglucose isomerase, phosphomannomutase, GDP-mannose pyrophosphorylase (GMPase), or GDP-D-mannose-3,5-epimerase increases the levels of levels of vitamin C in a plant and increasing the resistance to environmental stress, this would be inherent features of the plants of parent claims 1 and 9 and an inherent result of the method of parent claims 16. Thus, claims 6-7, 13-14 and 20-21 fail to further limit claims 1, 9 and 16. If the plant is to have the claimed utility, then it must express the recombinant nucleic acid; thus, claims 5 and 12 fail to further limit claims 1 and 9. This objection replaces the objection set forth in the Office action mailed 31 December 2003, as applied to claims 6-7, 13-14 and 20-21. Applicant's arguments filed 22 April 2004 do not apply to this new objection.

Claim Rejections - 35 USC § 112

5. Claims 1-22 and 24-26 remain rejected under 35 U.S.C. 112, first paragraph, as containing subject matter that was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention. The rejection is modified from the rejection set forth in the Office action mailed 31 December 2003. Applicant's arguments and the Declaration of Dr. Patricia Conklin, both filed 22 April 2004, have been fully considered but they are not persuasive.

The claims are broadly drawn to a method of increasing the levels of vitamin C in a plant and increasing the resistance to environmental stress by expression a nucleic acid that encodes an enzyme in a plant biosynthetic pathway, wherein the enzyme is phosphoglucose isomerase, phosphomannomutase, GMPase, or GDP-D-mannose-3,5-epimerase, and plants thereby obtained.

The instant specification only provides guidance for EMS mutagenesis of *Arabidopsis* to produce two mutants, named *vtc*, that are deficient in AsA production (pg 7-9); testing the mutants for loss of conversion from mannose to ascorbic acid (pg 9-10); AFLP mapping of the *vtc* loci - *vtc1* maps within a published BAC that has as one of its open reading frames a putative mannose-1-phosphate guanyltransferase, aka GDP-mannose pyrophosphorylase, and for which a partial sequence has been published in GenBank as Accession No. T46645; this sequence is mutated in *vtc1-1* and *vtc1-2* (pg 10-12); measuring GDP-mannose pyrophosphorylase activity in *vtc1* mutants (pg 12-13); and complementation of the *vtc1-1* mutant with a 3.4 kb subfragment from the BAC clone that has the GDP-mannose pyrophosphorylase gene (pg 13-17).

The instant specification fails to provide guidance for the sequence of the full-length gene encoding GMPase, and thus provide guidance for wild-type plants transformed with the GMPase

gene and methods of making stress resistant plants by transformation with a nucleic acid encoding the GMPase gene. The specification also fails to provide guidance for nucleic acids encoding phosphoglucose isomerase, phosphomannomutase, or GDP-D-mannose-3,5-epimerase, and thus provide guidance for wild-type plants transformed with nucleic acids encoding phosphoglucose isomerase, phosphomannomutase, or GDP-D-mannose-3,5-epimerase and methods of making stress resistant plants by transformation with a nucleic acid encoding any of these enzymes.

The specification does not teach the sequence of full-length Arabidopsis GMPase gene. GenBank Accession No. T46645 is only 510 nucleotides long and only encodes a protein of 83 amino acids, as shown below:

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T46645

ATTTTGCCAACGAACGTTCTTTCTTCTTAATCACAGCNCAGCCTGACGCAACCGCTCAGGCTGATCTN
TTCCAATTTACAGCCATTTCCCAGCTCAGATCTCTGATCCGGTGAGATCTCTCTCAAGGAAAAGGAGT

TAGAGCATCATCAAGATGAAGGCACTCATTCTTGTTGGAGGCTTCGGCACTCGCTTGAGACCATTGAC
                MetLysAlaLeuIleLeuValGlyGlyPheGlyThrArgLeuArgProLeuTh

TCTCAGTTTCCCAAAGCCCCTTGTTGATTTTNCTAATAAACCCATGATCCTTCATCAGATAGAGGCTC
rLeuSerPheProLysProLeuValAspPheXXXAsnLysProMetIleLeuHisGlnIleGluAlaL

TTAAGGCAGTTGGAGTTGATGAAGTGGTTTTGGCCATCAATTATCAGCCAGAGGTGATGCTGAACTTC
euLysAlaValGlyValAspGluValValLeuAlaIleAsnTyrGlnProGluValMetLeuAsnPhe


TTGAAGGACTTTNAGACCAAGCTGGAAATCAAAATCACTTGCTCACAAGAGCCGAGCNACTAGGTACC
LeuLysAspPheXXXThrLysLeuGluIleLysIleThrCysSerGlnGluProSerXXXstp

GCTGGTCCTTGGTTTANNGGGNGCAAATTGNTTTATGGACCTGNGNGCCCTTTTTGTTTTAAAAGNNA
TGANTAAGGGGNCCCNNTAAANAANCTTNGGGTT
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The specification on pg 11, lines 3-15 states that the protein encoded by T46645 has 59% identity to the mannose-1-phosphate guanyltransferase from *Saccharomyces cerevisiae*. However, this enzyme from yeast is 361 amino acids long (Schultz et al, 2002, GenBank Accession No. P41940). T46645 only encodes a protein that is about 23% of the length of the yeast protein sequence. Thus, it is clear that T46645 does not encode a full-length enzyme.

The full length GMPase from Arabidopsis has been isolated since the filing of the instant specification. This sequence, NM_129535 (Town et al, 2002, GeneBank Accession No. NM_129535) is shown below, aligned with T46645 (T46645 is shown in bold, bases that do not match with NM_129535 are shown in lower case):

T46645 vs NM_129535

ATTTTGCCAACGAACGTTCTTTCTTCTTAATCACAGCNCAGCCTGACGCAACC
GCCTATCATTTTGCCAACGAACGTTCTTTCTTCTTAATCACAGCTCAGCCTGACGCAACC 60

GCTCAGGCTGATCTNTTCCAATTTACAGCCATTTCCCAGCTCAGATCTCTGATCCGGTGA
GCTCAGGCTGATCTCTTCCAATTTACAGCCATTTCCCAGCTCAGATCTCTGATCCGGTGA 120

GATCTCTCTCAAGGAAAAGGAGTTAGAGCATCATCAAGATGAAGGCACTCATTCTTGTTG
GATCTCTCTCAAGGAAAAGGAGTTAGAGCATCATCAAGATGAAGGCACTCATTCTTGTTG 180
MetLysAlaLeuIleLeuValG

CGAGGCTTCGGCACTCGCTTGAGACATTGACTCTCAGTTTCCCAAAGCCCCTTGTTGATT
GAGGCTTCGGCACTCGCTTGAGACCATTGACTCTCAGTTTCCCAAAGCCCCTTGTTGATT 240
lyGlyPheGlyThrArgLeuArgProLeuThrLeuSerPheProLysProLeuValAspP

TTNCTAATAAACCCATGATCCTTCATCAGATAGAGGCTCTTAAGGCAGTTGGAGTTGATG
TTGCTAATAAACCCATGATCCTTCATCAGATAGAGGCTCTTAAGGCAGTTGGAGTTGATG 300
heAlaAsnLysProMetIleLeuHisGlnIleGluAlaLeuLysAlaValGlyValAspG

AAGTGGTTTTGGCCATCAATTATCAGCCAGAGGTGATGCTGAACTTCTTGAAGGACTTTN
AAGTGGTTTTGGCCATCAATTATCAGCCAGAGGTGATGCTGAACTTCTTGAAGGACTTTG 360
luValValLeuAlaIleAsnTyrGlnProGluValMetLeuAsnPheLeuLysAspPheG

AGaccaaGCTGGaaaTCaaaaTCacttGctcacaAgagccgagcnactAggTaccgctg
TAGGTACCGCTGGTCCTCTGGCTCTAGCGAGAGACAAATTGCTTGATGGATCTGGAGAGC 420
euGlyThrAlaGlyProLeuAlaLeuAlaArgAspLysLeuLeuAspGlySerGlyGluP

gtcctTggtttannggGgnGcAAATtgnttTatggacCTgngngccctttttGttttaaaa
CCTTCTTTAGACCAAGCTGGAAATCAAAATCACTTGCTCACAAGAGACCGAGCCACGTTC 480
roPhePheluThrLysLeuGluIleLysIleThrCysSerGlnGluThrGluProLVal L

gnnAtgantAaGgggncccnntaaAnaanCTTnggGtt
TTAACAGTGATGTGATTAGTGAGTACCCTCTTAAAGAAATGCTTGAGTTTCACAAATCTC 540
euAsnSerAspValIleSerGluTyrProLeuLysGluMetLeuGluPheHisLysSerH

AACGGTGGGGAAGCCTCCATAATGGTAACAAAGGTGGATGAACCGTCGAAATATGGAGTG 600
isGlyGlyGluAlaSerIleMetValThrLysValAspGluProSerLysTyrGlyValV

GTTGTTATGGAAGAAGCACTGGAAGAGTGGAGAAGTTTGTGGAAAAGCCAAAACTGTATG 660
alValMetGluGluSerThrGlyArgValGluLysPheValGluLysProLysLeuTyrV

TAGGTAACAAGATCAACGCTGGGATTTATCTTCTGAACCCATCTGTTCTTGATAAGATTG 720
alGlyAsnLysIleAsnAlaGlyIleTyrLeuLeuAsnProSerValLeuAspLysIleG

AGCTAAGACCGACTTCAATCGAAAAAGAGACTTTCCCTAAGATTGCAGCAGCGCAAGGGC 780
luLeuArgProThrSerIleGluLysGluThrPheProLysIleAlaAlaAlaGlnGlyL

TCTATGCTATGGTGCTACCAGGGTTTTGGATGGACATTGGGCAACCCCGTGACTACATAA 840
euTyrAlaMetValLeuProGlyPheGlnMetAspIleGlyGlnProArgAspTyrIleT

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CGGGTTTGAGACTCTACTTAGACTCCCTTAGGAAGAAATCTCCTGCCAAATTAACCAGTG     900
hrGlyLeuArgLeuTyrLeuAspSerLeuArgLysLysSerProAlaLysLeuThrSerG

GGCCACACATAGTTGGGAATGTTCTTGTTGACGAAACCGCTACAATTGGGGAAGGATGTT     960
lyProHisIleValGlyAsnValLeuValAspGluThrAlaThrIleGlyGluGlyCysL

TGATTGGACCAGACGTTGCCATTGGTCCAGGCTGCATTGTTGAGTCAGGAGTCAGACTCT    1020
euIleGlyProAspValAlaIleGlyProGlyCysIleValGluSerGlyValArgLeuS

CCCGATGCACGGTCATGCGTGGAGTCCGCATCAAGAAGCATGCGTGTATCTCGAGCAGTA    1080
erArgCysThrValMetArgGlyValArgIleLysLysHisAlaCysIleSerSerSerI

TCATCGGGTGGCACTCAACGGTTGGTCAATGGGCCAGGATCGAGAACATGACGATCCTCG    1140
leIleGlyGlnHisSerThrValGlyGlnGlnAlaArgIleGluAsnMetThrIleLeuG

GTGAGGATGTTCATGTGAGCGATGAGATCTATAGCAATGGAGGAGTTGTTTTGCCACACA    1200
lyGluAspValHisValSerAspGluIleTyrSerAsnGlyGlyValValLeuProHisL

AGGAGATCAAATCAAACATCTTGAAGCCAGAGATAGTGATGTGAAAATGAGATATTATAT    1260
ysGluIleLysSerAsnIleLeuLysProGluIleValMet

GTGCAACTTTTTTTTTTTTTTTTGTGTCCTTTCTTCAACTTTGAAATCGCTTTCGTAATT    1320
CTTAATGGCTTTTGAATAAGCATCAATCAAAACGCTGTATATCTTGTTAGGGTCGTTTGC    1380
TGTTTTGTCTCTTTTTTTGTTTTGTAATTTATAAAAAAATTTATTCTCATTTTATGTGAG    1440
ATACTTTTGAATATTCATTAATTATAAAGCTTTTTTTTTGTGAAGTAA                1488
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It is clear from this alignment that T46645 does not encode the full-length GMPase sequence. Furthermore, the sequence differences between T46645 and NM_129535 mean that even within the portions of T46645 and NM_129535 that overlap, T46645 encodes a protein with a different amino acid sequence that does NM_129535. Thus, this sequence could not be used to produce plants with increased levels of vitamin C, nor could a plant transformed with a nucleic acid comprising T46645 have increased levels of vitamin C.

What Applicant transformed into the *vtc1* mutant was vector gVTC1-GPTV, which comprises a 3.4 kb DNA from the VTC1 locus (specification, pg 14, lines 1-6); this DNA is more than 6 times longer than the 510 nucleotides of T46645 and presumably comprises the full length GMPase as shown in NM_129535.

Furthermore, no nucleic acid encoding GDP-mannose epimerase was known at the time of filing. Wolucka et al (2001, Proc. Natl. Acad. Sci. USA 98:14843-14848) teach the first (pg

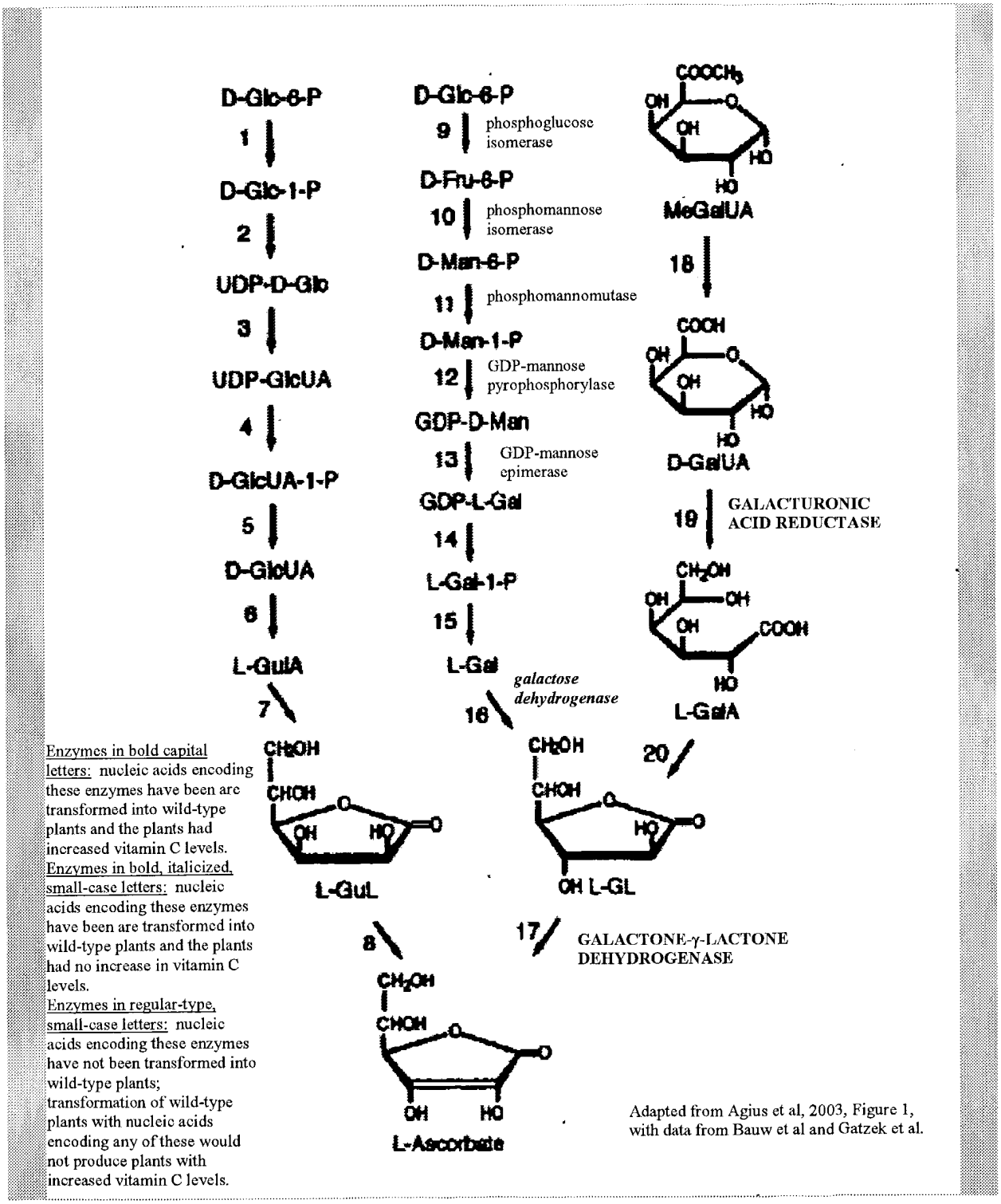
14844, left column, paragraph 1), two years after the filing of the instant application. The instant specification teaches no nucleic acid encoding GDP-mannose epimerase; thus, the specification cannot be enabled for plants transformed with a nucleic acid encoding GDP-mannose epimerase or for methods of producing those plants.

The specification fails to teach any nucleic acids encoding phosphoglucose isomerase or phosphomannomutase.

Davey et al (1999, Plant Physiol. 121:535-543) teach that there is more than one pathway for vitamin C synthesis in *Arabidopsis*; all of these pathways use L-galactone-1,4-lactone as the precursor before L-ascorbic acid, but they each produce L-galactone-1,4-lactone from very different precursors (Figure 4). Gatzek et al (2002, Plant J. 30:541-553) expressed in *Arabidopsis* plants a nucleic acid encoding L-galactose dehydrogenase, which is the second-to-last enzyme in the vitamin C biosynthesis pathway shown in the instant Figure 1. Although the enzyme level was increased 3.5 fold, there was no increase in vitamin C concentration in leaves (see abstract). In contrast, Agius et al (2003, Nature Biotechnol. 21:177-181) teach that expression of a nucleic acid encoding D-galacturonate reductase, an enzyme in one of the other pathways, in *Arabidopsis* plants did result in increased levels of vitamin C relative to wild-type plants (see abstract), and Bauw et al (WO 98/50558) teach that transformation of wild-type plants with a nucleic acid encoding L-galactono-g-lactone dehydrogenase also resulted in plants with increased vitamin C levels (pg 18, lines 28-31). These results suggest that expression of a nucleic acid encoding any of the enzymes before galactono-1,4-lactone dehydrogenase the vitamin C biosynthesis pathway shown in the instant Figure 1, including phosphoglucose isomerase, phosphomannomutase, GMPase, or GDP-mannose epimerase, would not increase vitamin C levels relative to those in

wild-type plants.

These results are summarized below:



Thus, it would not be possible to achieve an increased vitamin C concentration in plants by transformation with a nucleic acid encoding phosphoglucose isomerase, phosphomannomutase, GMPase, or GDP-mannose epimerase, and transformation with a nucleic acids encoding one of those enzymes would not result in increased vitamin C content or increased resistance to drought, cold, UV radiation, air pollution, salts, heavy metals and/or reactive oxygen species.

Applicant is invited to submit a Declaration showing that plants transformed with a nucleic acid encoding phosphoglucose isomerase, phosphomannomutase, GMPase, or GDP-mannose epimerase behave differently than plants transformed other nucleic acids encoding the enzymes before galactono-1,4-lactone dehydrogenase in the vitamin C pathway of in the instant Figure 1 and have increased levels of vitamin C and increased stress resistance relative to wild-type plants. This Declaration, however, will not enable the nucleic acid encoding GMPase from Arabidopsis or GDP-mannose epimerase from any source. Only a deposit of pVTC1-GPTV, as below, will enable the nucleic acid encoding GMPase from Arabidopsis. A nucleic acid encoding GDP-mannose epimerase cannot be enabled, given it was not known in the prior art.

If the deposit is made under the terms of the Budapest Treaty, then an affidavit or declaration by Applicant, or a statement by an attorney of record over his or her signature and registration number, stating that the specific strain has been deposited under the Budapest Treaty and that the strain will be irrevocably and without restriction or condition released to the public upon the issuance of a patent, would satisfy the deposit requirement made herein.

If the deposit has not been made under the Budapest Treaty, then in order to certify that the deposit meets the criteria set forth in 37 C.F.R. 1.801-1.809, Applicant may provide assurance of compliance by an affidavit or declaration, or by a statement by an attorney of record over his or her signature and registration number, showing that

(a) during the pendency of this application, access to the invention will be afforded to the Commissioner upon request;
(b) all restrictions upon availability to the public will be irrevocably removed upon granting of the patent;

(c) the deposit will be maintained in a public depository for a period of 30 years or 5 years after the last request or for the enforceable life of the patent, whichever is longer;
(d) a test of the viability of the biological material at the time of deposit (see 37 CFR 1.807); and,
(e) the deposit will be replaced if it should ever become inviable.

Given the claim breath, unpredictability, and lack of guidance as discussed above, undue experimentation would have been required by one skilled in the art to develop and evaluate methods for increasing the endogenous level of vitamin C and resistance to environmental stresses in a plant by expression by of a nucleic acid encoding phosphoglucose isomerase, phosphomannomutase, GMPase, or GDP-mannose epimerase.

Applicant urges that a full-length GMPase sequence is not required to enable the instant invention since one of ordinary skill in the art would not need to perform undue experimentation to practice the invention (response pg 9).

This is not found persuasive because a full-length GMPase enzyme cannot be made from the partial sequence disclosed in the specification.

Applicant and the Declaration urge that the specification provides guidance for the full-length gene encoding GMPase (response pg 10, Declaration ¶11).

This is not found persuasive because the specification does not teach the sequence of the full-length coding sequence of the GMPase gene.

Applicant and the Declaration urge that the *vtc1* mutant was mapped and that analysis of the mutant showed it incorporated less mannose into ascorbic acid than did wild-type. Applicant and the Declaration urge that an EST (GenBank Accession No. T46445) was found that was annotated as being a putative glucose-1-P thymidylyltransferase and that no experimentation

would be required to identify the EST. Applicant and the Declaration urge that this EST aligned with yeast vig9 (response pg 10-11, Declaration ¶13-16)

This is not found persuasive because GenBank Accession No. T46645 is only 510 nucleotides long and only encodes a protein of 83 amino acids; T46645 only encodes a protein that is about 23% of the length of the yeast protein sequence.

Applicant and the Declaration urge that the EST was used to search the Arabidopsis Genebank to find BAC T517 via a BLAST query; the date the sequence was available is 1997. Applicant and the Declaration urge that the sequence of this BAC is not required to practice the invention. The Declaration urges that one of skill in the art could obtain T46645 from the Arabidopsis Biological resource Center (response pg 11, Declaration ¶17-21).

This is not found persuasive because T46645 is only 510 nucleotides long and only encodes a protein of 83 amino acids and does not encode a full-length enzyme. Even if transformation of a wild-type plant with a nucleic acid encoding GMPase increased vitamin C levels in the transgenic plant, transformation with T46645 would not do so. Either the sequence of BACT517 is required or BACT517 must be available.

None of the BLAST results submitted by applicant indicates that the full-length GMPase sequence, as opposed to a partial sequence, was available at the time of filing.

Applicant urges that a 5.4 ClaI fragment was subcloned from BAC T517, which was further subcloned to make the vector used to complement the vtc1-1 mutant. Applicant urges that the gene was available at the time of filing, within BAC T517, and that a requirement that the sequence be known at the time of filing it not consistent with the law of enablement (response pg 11-12).

This is not found persuasive. Either the sequence must be known, or BACT517 must be deposited under the Budapest treaty.

Applicant urges that BACT517 was identified in the specification and available at the time of filing, and is still available today from the ABRC; as the size of the fragment used was disclosed in the specification, one of skill in the art could practice the invention with no experimentation. Applicant urges that they do not have to prove that BACT517 would be available 30 years from unless there is a reasonable basis to believe that the biological material will cease to be available during the enforceable life of the patent (response pg 12).

This is not found persuasive. The ABRC Stock Acquisition and Deacquisition Policy states that they may maintain a stock but forgo distribution, may discard a stock, or may replace a stock with a different one (see http:www.Arabidopsis.org/abrc/acquis_deacquis.jsp, pg 4). The ABRC Stock Acquisition and Deacquisition Policy provides a reasonable basis to believe that the biological material will cease to be available to the public during the enforceable life of the patent. Thus, current availability of BACT517 at ABRC is not sufficient to satisfy the enablement requirement.

Applicant urges that the specification provides ample guidance for the full-length gene encoding GMPase, via the recitation that VTC1 was fine-mapped within a 2Mb region; one of skill in the art could create a genetically engineered plant as recited in the claims without undue experimentation (response pg 13).

This is not found persuasive because the instant claims are not drawn to a method of increasing vitamin C levels and increasing stress resistance in a plant by transformed with the

VTC4 gene and plants thereby obtained. Furthermore, as detailed in the enablement rejection for that abandoned application, that invention was also not enabled.

Applicant and the Declaration urge that the specification teaches plants transformed with the GMPase gene, wherein the plants have increased vitamin C levels (response pg 13, Declaration ¶23, 25).

This is not found persuasive. Applicant on pg 16-17 transformed a mutant *vtc1-1* plant with a GMPase clone, effectively converting a mutant plant into a wild-type plant. This procedure is called complementation and the experiment merely showed that the clone was from the vtc1 gene. If the experiment had been unsuccessful, it would have merely shown the cDNA was not from the vtc1 gene.

Dong et al (2001, Plant Physiol. 127:46-57) teach that when genes encoding enzymes in one biosynthetic pathway are overexpressed in wild-type plants, there was no increase in the levels of end product of the pathway, even those genes complemented mutants in the pathway (see abstract). Thus, just because a nucleic acid complements a mutant, overexpression of that gene in wild-type plants will not necessarily result in an increase in the levels of end product of the pathway.

Applicant did not transform a wild-type plant with the GMPase cDNA clone to show that the plants so produced have increased levels of vitamin C relative to wild-type plants. Furthermore, Applicant did not use a clone where the only GMPase sequence was that of T46645. It is suggested that Applicant submit a Declaration showing that plants transformed with a nucleic acid encoding phosphoglucose isomerase, phosphomannomutase, T46645, or

GDP-mannose epimerase have increased levels of vitamin C and increased stress resistance relative to wild-type plants.

Applicant urges that in a prior Office action asserted that Bauw et al (WO98/50558) teach plants transformed with a nucleic acid encoding L-galactone-y-lactone dehydrogenase and that these plants inherently have increased vitamin C levels; thus, it was acknowledged that it was possible to produce plants with increased vitamin C levels (response pg 14).

This is not found persuasive. The rejection is not that it is impossible to produce plants with increased vitamin C levels, just that it was impossible to do so as claimed.

Applicant and the Declaration urge that the extensive teachings in the art combined with the teachings in the specification make it clear that a wide variety of plants can be transformed with a gene in the vitamin C biosynthetic pathway to increase levels of vitamin C in plants (response pg 14, Declaration ¶26).

This is not found persuasive. First, the only plant successfully transformed with a gene in the vitamin C biosynthetic pathway to increase levels of vitamin C in plants is *Arabidopsis*. Second, the teachings in the art make it clear that not all genes in the vitamin C biosynthetic pathway can be successfully increase levels of vitamin C in plants (see, *e.g.*, Gatzek et al). The specification does not overcome the teachings in the art, for the reasons detailed above.

Applicant and the Declaration urge that following the teachings in the specification they narrowed another locus with probable involvement in the vitamin C biosynthesis pathway to a small region in the Arabidopsis genome in an application filed as 09/909,600; thus, the instant specification provides enablement for the claimed invention (response pg 14, Declaration ¶22).

This is not found persuasive. The instant specification provides no guidance for the vtc4 gene.

Applicant urges that the specification clearly teaches a transgenic plant that had increased vitamin C levels relative to a progenitor plant (response pg 15-17).

This is not found persuasive. The claims encompass wild-type plants transformed with a nucleic acid encoding GMPase, as well as *vtc1-1* plants transformed with a nucleic acid encoding GMPase. The teachings of Gatzek et al indicate unpredictability associated with transformation of wild-type plants with nucleic acid encoding enzymes in the pathway of the instant Figure 1. Nothing Applicant has done overcomes that unpredictability. It is suggested that Applicant overcome that unpredictability by submitting a Declaration showing that wild-type plants transformed with a nucleic acid encoding phosphoglucose isomerase, GMPase, phosphomannomutase, or GDP-mannose epimerase have increased levels of vitamin C relative to untransformed wild-type plants.

Applicant urges, in response to a statement that were was no use for a mutant plant complemented by the nucleic acid, that no utility rejection was made (response pg 17).

This is not found persuasive. The enablement requirement has two prongs, how to make and how to use. As the mutant plant complemented by the nucleic acid is identical to a wild-type plant, there is no specific and substantial use for such a plant. The *vtc1-1* plants transformed with pVTC1-GPTV had only wild-type levels of vitamin C (specification, pg 16, lines 1-2); no plants were obtained with levels greater than those in wild-type. There is no specific and substantial use for a plant with wild-type levels of vitamin C.

Applicant urges that they only have to enable the claimed subject matter, and they have enabled the claims by showing that a plant comprising a nucleic acid encoding an enzyme in a plant vitamin C pathway [sic]; the examiner cannot decide an example is inadequate when it enables the claimed subject matter (response pg 17).

This is not found persuasive. The example is inadequate because the totality of the following indicate that the specification is not enabled: *vtc1-1* plants transformed with pVTC1-GPTV had only wild-type levels of vitamin C; nucleic acid encoding GMPase and GDP-mannose epimerase were not available at the time of filing; the teachings of Gatzek et al indicate unpredictability associated with transformation of wild-type plants with nucleic acid encoding enzymes in the pathway of the instant Figure 1; and Applicant has provided no evidence that wild-type plants transformed with a nucleic acid encoding phosphoglucose isomerase, GMPase, phosphomannomutase, or GDP-mannose epimerase have increased levels of vitamin C relative to untransformed wild-type plants.

Applicant urges that the Office action mailed 24 July 2001 stated that the plants of Trulson et al, which were dicots transformed with a nucleic acid encoding phosphomannose isomerase, would inherently have increased stress resistance and vitamin C levels, but in the Office action mailed 31 December 2003, states that in light of the teachings of Gatzek et al that plants transformed with a nucleic acid encoding phosphomannose isomerase, would inherently have increased stress resistance and vitamin C levels; Applicant requests additional evidence to support the arguments that Gatzek nullifies the previous statement (response pg 18).

This is not found persuasive. The teachings of Gatzek et al, 2002, were not available at the time of the Office action mailed July 2001; if they had been, the statement would not have been made. No additional evidence is required.

Applicant urges that Gatzek et al merely shows that an increase in enzyme levels for L-galactose dehydrogenase did not increase vitamin C levels in leaves, Davey et al merely shows that there is more than one vitamin C biosynthesis pathway, and Agius shows that overexpression of an enzyme in one of the other pathways increases vitamin C biosynthesis. Applicant urges that the conclusion that since one of the enzymes in Applicant's pathway did not work, the others would not is unwarranted and no concrete evidence was provided to support the conclusion. Applicant urges that another conclusion from the Gatzek results is that the rate-limiting step is before galactono-1,4, lactone dehydrogenase. Applicant also urges that plants transformed with a nucleic acid encoding GMPase have increased vitamin C levels compared to the progenitor plants (response pg 18-19).

This is not found persuasive. The results of Gatzek et al, in conjunction with those of Bauw et al, provide a strong expectation that since one of the enzymes in Applicant's pathway did not work, the ones before in the pathway also would not. The data from Gatzek et al and Bauw et al indicate that the rate-limiting step is not before galactono-1,4, lactone dehydrogenase, as follows: Transformation of plants with a nucleic acid encoding L-galactose dehydrogenase may not result in increased levels of vitamin C either because the upstream enzymes are not producing enough substrate, galactose, or because the next enzyme in the pathway cannot use the product, galactono-1,4-lactone, at higher than wild-type levels. Bauw et al transformed plants with a nucleic acid encoding galactono-1,4-lactone dehydrogenase, which converts galactono-

1,4-lactone to vitamin C; levels of vitamin C in those plants with higher than wild-type levels (pg 18, lines 28-31). Thus, transformation of plants with a nucleic acid encoding L-galactose dehydrogenase did not result in increased levels of vitamin C because there is not enough galactono-1,4-lactone dehydrogenase in wild-type plants. Transformation with a nucleic acid encoding an enzyme upstream of L-galactose dehydrogenase in the pathway of the instant Figure 1 would not result in an increase in vitamin C levels in a wild-type plant. Additionally, Applicant arguments that the rate-limiting step is before galactono-1,4, lactone dehydrogenase, even if true, would not indicate that transformation of a plant with a nucleic acid encoding phosphoglucose isomerase, GMPase, phosphomannomutase, or GDP-mannose epimerase would work. Lastly, it is noted that none of the transformants produced by Applicant's transformation of *vtc1-1* with pVTC1-GPTV had higher than levels of vitamin C, as would be expected if transformation with a nucleic acid encoding GMPase could increase vitamin C levels above wild-type levels.

Applicant urges that they have enabled the invention by providing a real example supporting the claims as written (response pg 19).

This is not found persuasive. The claims encompass wild-type plants transformed with a nucleic acid encoding GMPase, as well as *vtc1-1* plants transformed with a nucleic acid encoding GMPase. *vtc1-1* plants transformed with a nucleic acid encoding GMPase only had wild-type levels of vitamin C; unexpectedly, none overproduced vitamin C.

To reiterate: Nucleic acids encoding GDP-mannose epimerase were not available at the time of filing. Nucleic acids encoding GMPase do not appear to have not available at the time of filing, and T46445 is only a partial sequence. No plant transformed with a nucleic acid

comprising T46445 could produce GMPase because the sequence of T46445 has so many errors. The specification teaches no nucleic acid encoding phosphoglucose isomerase or phosphomannomutase. The teachings of Gatzek et al indicate unpredictability associated with transformation of wild-type plants with nucleic acid encoding enzymes in the pathway of the instant Figure 1. Applicant has not provided evidence that wild-type plants transformed with a nucleic acid encoding phosphoglucose isomerase, GMPase, phosphomannomutase, or GDP-mannose epimerase have increased levels of vitamin C relative to untransformed wild-type plants.

It is noted that in the interview of 13 April 2004 that applicant's representative stated that the inventor was no longer working on this invention. However, submission of data showing that wild-type plants transformed with a nucleic acid encoding phosphoglucose isomerase, GMPase, phosphomannomutase, or GDP-mannose epimerase have increased levels of vitamin C relative to untransformed wild-type plants would overcome a large portion of this enablement rejection.

6. Claims 1-22 and 24-26 are rejected under 35 U.S.C. § 112, first paragraph, as containing subject matter that was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. The rejection is modified from the rejection set forth in the Office action mailed 31 December 2003. Applicant's arguments and the Declaration of Dr. Patricia Conklin, both filed 22 April 2004 have been fully considered but they are not persuasive.

The claims are broadly drawn to methods of using a multitude of nucleic acids encoding phosphoglucose isomerase, phosphomannomutase, GDP-mannose epimerase or GMPase. The

specification describes no nucleic acids encoding plant phosphoglucose isomerases, phosphomannomutases or GDP-mannose epimerases. The specification only describes a nucleic acid a partial, and incorrectly sequence, nucleic acid encoding a portion of a GMPase enzyme. Applicant does not describe other nucleic acids encompassed by the claims, and the structural features that distinguish all such nucleic acids from other nucleic acids are not provided.

No genes encoding GDP-mannose epimerase were known at the time of filing (see Wolucka et al, pg 14844, left column, paragraph 1). It is not clear that any plant nucleic acids encoding phosphoglucose isomerase or phosphomannomutase, or if any other plant GMPAses were known at the time of filing. Even if some genes encoding phosphoglucose isomerase, phosphomannomutase or GMPase were known, such sequences do not describe the full scope of genes encoding phosphoglucose isomerase, phosphomannomutase or GMPase.

Because the sequences are not described, the method of using the sequences to make plants with increased vitamin C levels is likewise not described, and the specification fails to provide an adequate written description of the claimed invention.

Therefore, given the lack of written description in the specification with regard to the structural and physical characteristics of the compositions used in the claimed methods, it is not clear that Applicant was in possession of the genus claimed at the time this application was filed.

Applicant and the Declaration urge that many of the genes encoding GMPase, including Arabidopsis, and the other enzymes in the vitamin C pathway are known in the art (response pg 21, Declaration ¶27).

This is not found persuasive. Applicant provides no sequences supporting their assertion that many of the genes encoding GMPase, including Arabidopsis, and the other enzymes in the

vitamin C pathway are known in the art. The coding sequence of full-length Arabidopsis GMPase gene was not known in the prior art. Furthermore, Applicant has provided no evidence that any plant genes encoding phosphoglucose isomerase or phosphomannomutase were known at the time of filing, and certainly no genes encoding GDP-mannose epimerase from any source were known at the time of filing (see Wolucka et al, pg 14844, left column, paragraph 1). Lastly, even if some genes encoding phosphoglucose isomerase, phosphomannomutase or GMPase were known, such sequences do not describe the full scope of genes encoding phosphoglucose isomerase, phosphomannomutase or GMPase.

Applicant and the Declaration urge that Figure 1 and the specification on pg 4 disclose the enzymes in the vitamin C pathway (response pg 21 and Declaration ¶28).

This is not found persuasive. Disclosure of a list of enzyme names does not describe the structural features, that is, the sequence, of the nucleic acids that encode such enzymes.

The Declaration urges that one of skill in the art would know that they were in possession of possession of the invention from the pathway in Figure 1; sequences of those enzymes would not be required to clone a nucleic acid encoding an enzyme in a Vitamin C biosynthetic pathway or express the enzyme in a plant (Declaration ¶29).

This is not found persuasive. Patent law requires a functional and structural description of a composition and of compositions used in a method. The list of enzymes in Figure 1 is merely a functional description.

See *Univ. of California v. Eli Lilly*, 119 F.3d 1559, 43 USPQ 2d 1398 (Fed. Cir. 1997) at pg 1406:

> a generic statement such as "vertebrate insulin cDNA" or "mammalian insulin cDNA," without more, is not an adequate written description of the genus because it does not distinguish the genus from others, except by function. It does not specifically define any of the genes that fall within its definition. It does not define any

> structural features commonly possessed by members of the genus that distinguish them from others. One skilled in the art therefore cannot, as one can do with a fully described genus, visualize or recognize the identity of the members of the genus. A definition by function, as we have previously indicted, does not suffice to define the genus because it is only an indication of what the genes does, not what it is.
> ... A description of a genus of cDNAs may be achieved by means of a recitation of a representative number of cDNAs, defined by nucleotide sequence, falling within the scope of the genus or of a recitation of structural features common to the members of the genus, which features constitute a substantial portion of the genus.
> ... the claimed genera of vertebrate and mammal cDNA are not described by the general language of the '525 patent's written description supported only by the specific nucleotide sequence of rat insulin.

See *Amgen Inc. v. Chugai Pharmaceutical Co. Ltd.*, 18 USPQ 2d 1016 at page 1021:

> A gene is a chemical compound, albeit a complex one, and ... conception of a chemical compound requires that the inventor be able to define it so as to distinguish it from other materials .... Conception does not occur unless one has a mental picture of the structure of the chemical or is able to define it by its method of preparation, its physical or chemical properties, or whatever characteristics sufficiently distinguish it. It is not sufficient to define it solely by it principal biological property, *e.g.*, encoding human erythropoietin, because an alleged conception having no more specificity than that is simply a wish to know the identity of any material with that biological property.

See *University of Rochester v. G.D. Searle & Co.*, 69 USPQ2d 1886 (CA FC 2004) at page 1894:

> Rochester also attempts to distinguish Fiers, Lilly, and Enzo by suggesting that the holdings in those cases were limited to composition of matter claims, whereas the '850 patent is directed to a method. We agree with the district court that that is "a semantic distinction without a difference." Univ. of Rochester, 249 F. Supp. 2d at 228. Regardless whether a compound is claimed per se or a method is claimed that entails the use of the compound, the inventor cannot lay claim to that subject matter unless he can provide a description of the compound sufficient to distinguish infringing compounds from non-infringing compounds, or infringing methods from non-infringing methods. As the district court observed, "[t]he claimed method depends upon finding a compound that selectively inhibits PGHS-2 activity. Without such a compound, it is impossible to practice the claimed method of treatment."

Applicant urges that the specification provides ample guidance for the sequence of the GMPase gene and had they possession of the claimed invention as evidenced by identification and usage of BACT517 to obtain a subclone containing VTC1 (response pg 21).

This is not found persuasive because the specification does not provide an adequate written description of BACT517, the GMPase gene, or nucleic acids encoding phosphoglucose isomerase, phosphomannomutase or GDP-mannose epimerase.

7. Claims 1-8, 10, 16-22 and 24-26 remain rejected under 35 U.S.C. § 112, second

paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter that Applicant regards as the invention. Dependent claims are included in all rejections. The rejection is repeated for the reasons of record as set forth in the Office action mailed 31 December 2003. Applicant's arguments and the Declaration of Dr. Patricia Conklin, both filed 22 April 2004 have been fully considered but they are not persuasive.

Claim 1 remains indefinite in its recitation of "plant Vitamin C biosynthesis pathway." It is not clear if this means the nucleic acid is derived from plants or if the nucleic acid encodes any pathway enzyme that can function in plants.

Applicant and the Declaration urge that the enzymes encompassed by the claims are described in Figure 1 and the source of nucleic acids that encode these enzyme is not relevant since the claims have no limitation as to source (response pg 22 and Declaration ¶31).

This is not found persuasive. As currently written the enzymes are limited to plant enzymes because only a plant enzyme would be a plant biosynthetic pathway; a bacterial, fungal or animal enzyme would not. If Applicant wishes to limit their invention to plant enzymes then they should so state, and the rejection will be withdrawn. If, as suggested by the statements on pg 22 of the response and ¶31 of the Declaration, Applicant wishes to encompass enzymes from any source, the claim must be written differently (and without adding new matter).

The term "increasing" in claim 16 is a relative term that renders the claim indefinite. The term "increasing" is not defined by the claim, the specification does not provide a standard for ascertaining the requisite degree, and one of ordinary skill in the art would not be reasonably apprised of the scope of the invention. It is suggested that the level of vitamin C be compared to that of a wild-type plant.

Applicant and the Declaration urge one of ordinary skill in the art would understand the meaning of the term and apply its plain ordinary meaning; thus there is no need to define the term as everyone would understand the plants have increased vitamin C relative to untransformed plants (response pg 23 and Declaration ¶32).

This is not found persuasive because relative terms must be defined by the claim or the specification must provide a standard for ascertaining the requisite degree. Comparison to untransformed plants would define the term in the claim. It is noted that comparisons to untransformed plants are already made for the plants of claims 6-7 and 13-14 and for method claims 20-21, both of which are dependent upon claim 16. Claims 20-21 fail to further limit claim 16, as discussed above.

Claim Rejections - 35 USC § 102

8. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (e) the invention was described in a patent granted on an application for patent by another filed in the United States before the invention thereof by the applicant for patent, or on an international application by another who has fulfilled the requirements of paragraphs (1), (2), and (4) of section 371(c) of this title before the invention thereof by the applicant for patent.

9. Claims 1-2, 4-10, 12-18 and 20-22 are rejected under 35 U.S.C. 102(e) as being anticipated by Dhugga et al (US Patent 6,706,951, filed August 1998, see provisional Application 60/096,782).

Dhugga et al claim dicot and monocot plants transformed with a nucleic acid encoding a maize GDP-mannose pyrophosphorylase (claims 9-13). If transformation of a plant with a

nucleic acid encoding a maize GDP-mannose pyrophosphorylase increases the level of vitamin C in the plant, then these plants would inherently have increased levels of vitamin C relative to a nontransformed plant. Methods of producing those plants would involve transformation with a nucleic acid encoding the maize GDP-mannose pyrophosphorylase and expressing the enzyme in the plant, given that the plants of the claims are transformed with a construct comprising the nucleic acid operatively linked to a promoter; thus, the Dhugga et al teach a method whose steps are identical to the instant methods. Ff transformation of a plant with a nucleic acid encoding a maize GDP-mannose pyrophosphorylase increases the level of vitamin C in the plant, then this method would inherently be one of producing plants with increased levels of vitamin C.

Claim Rejections - 35 USC § 103

10. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

11. Claims 1-22 are rejected under 35 U.S.C. 103(a) as being unpatentable over Dhugga et al (US Patent 6,706,951).

The claims are drawn to *Arabidopsis* plants transformed with a nucleic acid encoding GMPase and methods of producing those plants.

The teachings of Dhugga et al are discussed above. Dhugga et al do not disclose *Arabidopsis* plants transformed with a nucleic acid encoding GMPase.

At the time the invention was made, it would have been obvious to one of ordinary skill in the art to modify the method of transform plants with a nucleic acid encoding GMPase as taught by Dhugga et al, to transform *Arabidopsis* plants with a nucleic acid encoding GMPase. One of ordinary skill in the art would have been motivated to do so because the significance of *Arabidopsis* in basic biological research.

Conclusion

12. No claim is allowed.

13. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Anne R. Kubelik, whose telephone number is (571) 272-0801. The examiner can normally be reached Monday through Friday, 8:30 am - 5:00 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Amy Nelson, can be reached at (571) 272-0804. The fax phone number for the organization where this application or proceeding is assigned is (703) 872-9306.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to (571) 272-0547.

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Anne R. Kubelik, Ph.D.
June 21, 2004

ANNE KUBELIK
PATENT EXAMINER